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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,633	11/25/1997	ELAZAR RABBANI	ENZ-53	4639

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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	
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09/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,633	RABBANI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *245-255,257-265 and 306* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *245-255,257-265 and 306* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-24-08, 3-7-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 8-24-08.

Claims 245-255, 257-265, and 306 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8-24-08 has been entered.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 245-255, 257-265, and 306 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, essentially for the reasons of record as set forth in the Office Action mailed 2-25-08 and for the reasons set forth below.

The claims are drawn to constructs comprising at least one terminus comprising any polynucleotide tail hybridized to any complementary polynucleotide sequence and any antibody bound to the hybridized polynucleotide sequence, which construct is bound non-ionically to any entity comprising a chemical modification or any ligand. The claims are also drawn to methods of delivery in vitro and in vivo of compositions comprising any non-natural entity comprising at least one domain to any specific nucleic acid component and one domain to any cell of interest, which domains are different from each other, and which entity further comprises a binder which is optionally the same as one of the two domains or different from these domains, wherein the domains are attached covalently or noncovalently or through the binder, or a combination of these, or which binder optionally comprises a modified polylysine, and which compositions optionally further comprise a cell of interest. The claims are also drawn to kits comprising a non-natural entity comprising at least one domain to any specific nucleic acid component and at least one domain to any cell of interest, a specific nucleic acid component and buffers and instruction, wherein the nucleic acid component is any nucleic acid sequence desired be delivered to a cell, wherein the domain or domains to

said nucleic acid component are different from the domain or domains to said cell, and wherein the specific nucleic acid component is bound to said entity through the domain to a specific nucleic acid component.

Applicant's arguments filed 8-24-08 have been fully considered but they are not persuasive. Applicants argue that adequate description has been provided for the genus of compounds claimed, including as provided in Figure 15 and example 12, and pages 51-55 of the specification. Applicant also argues that the particular nucleic acid is not a critical feature of the instant invention, but is defined broadly as a nucleic acid construct that is desired to be transported into a target cell.

Contrary to Applicant's assertions, one of skill in the art would not be able to readily recognize the genus of species encompassed by the claims based merely on the schematic drawings, which do not clearly demonstrate adequate description of the entire genus of species encompassed by the claims. As previously indicated, the specification as filed does not adequately describe a representative number of species of the claimed invention unless one of skill in the art would be able to envisage the structure, in this case the chemical structure (nucleic acid, protein, and other claimed chemical compositions, including the cells), of the claimed invention. Since none of the examples, either prophetic or exemplified by reduction to practice, in the specification as filed provide a clear description of the genus and species within the genus of the claimed invention, one of skill in the art would not have recognized that application was in possession of a representative number of species of the claimed invention at the time the invention was made.

Applicants contend that a detailed description of the compositions of the present invention is provided on pages 48-59, particularly pages 50-55. The terms "nucleic acid component", "domain", and "binder" are clearly defined on pages 48-49, and various examples of useful domains are described. Examples of various antibodies are provided in the paragraph bridging 53 and 54. These include useful domains with non-specific cell binding properties (see page 53), useful domains with specific cell binding properties (see page 53), useful domains with specific nucleic acid component binding properties (see page 54). Applicants also assert that the specification describes specific embodiments. Contrary to Applicant's assertions, the embodiments disclosed in the instant specification are not specific, as they only provide general guidance as to what broad types of compositions are instantly claimed. The descriptions in both the specification and in the figures do not provide an adequate description of specific species, nor representative number of such species, of compositions which may be envisioned to produce a product in a cell as claimed.

No concise structural features are provided for concisely identifying members of this genus, for instance, for this broad genus comprising any non-natural entity with at least one domain to any specific nucleic acid component and one domain to any cell of interest, which domains are different from each other, and which entity further comprises a binder which is optionally the same as one of the two domains or different from these domains, wherein the domains are attached covalently or noncovalently or through the binder, or through a combination of these, or which binder optionally comprises a modified polylysine, and which compositions optionally further comprise a

cell of interest. The genus encompassed by the generic language of the claims is so broad that one of skill in the art would not be able to distinguish species that exist outside of the genus from those encompassed within the genus. The genus encompasses essentially any nucleic acid sequence of any length, or multiple sequences of any lengths, including random sequences, sequences homologous to a gene of interest, and/or sequences partially homologous to a gene of interest. The genus also encompasses any type of cell, prokaryotic or eukaryotic, any chemical modification, any ligand, and includes the a few or possibly many domains which are optionally joined in any number of ways, including covalently or non-covalently. One of skill in the art would not be able to concisely determine what is encompassed by the expansive genus of compounds and compositions claimed.

For these reasons, the instant rejection is maintained.

Claims 263-265 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of selectively expressing a nucleic acid product in a cell in cell culture (in vitro), does not reasonably provide enablement for methods of expressing a nucleic acid product in a whole organism (in vivo). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, essentially for the reasons of record as set forth in the Office Action mailed 2-25-08 and for the reasons set forth below.

The claims are also drawn to methods of delivery in vitro and in vivo of compositions comprising any non-natural entity comprising at least one domain to any specific nucleic acid component and one domain to any cell of interest, which domains are different from each other, and which entity further comprises a binder which is optionally the same as one of the two domains or different from these domains, wherein the domains are attached covalently or noncovalently or through the binder, or a combination of these, or which binder optionally comprises a modified polylysine,

Applicant's arguments filed 8-24-08 have been fully considered but they are not persuasive. Applicant argues that the entire scope of the instant invention was fully enabled at the time of filing, and that various domains with specific cell binding properties are disclosed in the specification. Applicant also submitted several references that illustrate ligand based gene transfer in vivo.

In response, the references have been considered but do not overcome the art-recognized problems previously and repeatedly indicated. Shortcomings in gene therapy approaches include the unpredictability in providing adequate quantities of nucleic acid therapeutics by delivery specifically to desired target cells in a subject, unpredictability in reaching a desired subcellular target site, e.g., in the cytoplasm or nucleus and the ability to find and bind the target site and simultaneously avoid non-specific binding (see, e.g., Branch and Ma).

The claims are very broad. They are drawn to the ability to successfully and predictably deliver an expansive genus of compounds to any target cell in vitro or in an

organism. The ability to deliver adequate quantities of nucleic acids or therapeutic molecules to any target cell in an organism remains a highly unpredictable endeavor.

For these reasons, the instant rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 245-255, 257-260, 262, and 306 are rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al. (U.S. Patent 5,574,142), for the reasons of record set forth in the Office Action mailed 2-25-08 and as set forth below.

Meyer et al. (U.S. Patent 5,574,142) teach target cells for delivering compositions, and kits for target cell delivery, which compositions comprise a construct having at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide and an antibody bound to the hybridized polynucleotide (e.g. ribozymes attached to antibodies), which construct is optionally bound non-ionically to a ligand, and teaches compositions which optionally comprise a domain to a specific nucleic acid component and a domain to a cell of interest, and a different, specific nucleic acid desired to be delivered to said cell, and optionally comprising a

binder which is optionally the same as the domain to a cell of interest, or a polylysine, or one which mediates ligand binding to a receptor, including lectins, antigens (see esp. the abstract; Figures 1, 2, 4, 8, 9, 10; col. 1-6; 10; 12; 17-20; claims 1-5, 8, 9).

Applicant's arguments filed 8-24-08 have been fully considered but they are not persuasive. Applicant argues that Meyer does not properly anticipate the instantly claimed invention because all three elements are not disclosed in a single composition. Applicant asserts that the antisense taught by Meyer is not both a domain to a specific nucleic acid of interest and a nucleic acid of interest. Applicant points out that the disclosure of an antisense ODN, for instance, would not satisfy the three component requirement set forth in the amended claims, because the antisense would only satisfy the specific nucleic acid component, not both the specific nucleic acid component and a domain to a specific acid component.

Contrary to Applicant's assertions, Meyer is not limited to teaching antisense ODNs as part of the cell delivery compounds. Rather, Meyer teaches an array of components that are contemplated as being components of the cell delivery systems as instantly claimed. They include ribozymes, which comprise domains to a specific nucleic acid component (the non-binding domains of the ribozyme) and a specific nucleic acid (the target binding domain of the ribozyme), as well as including triplex DNA optionally comprising alkylating groups, cleaving groups or other functional groups, which comprise domains to a specific nucleic acid component (the non-target binding strands, or functional groups, as well as the specific nucleic acid component (the target binding domain). Furthermore, it is noted that the domain of a nucleic acid that is

involved in being covalently or non-covalently linked to either the targeting ligand or peptide domain of the cell delivery system taught by Meyer is not necessarily the domain that participates in target binding, once delivered to the target molecule, since this portion or domain to the nucleic acid would not have target binding capacity, due to its chemical modification, also qualifying this derivatized portion of oligonucleotides as a domain to the nucleic acid, but not the specific nucleic acid domain.

For these reasons, Meyer et al properly anticipate the instantly claimed invention.

New Objections/Rejections

Claim Objections

Claims 247 is objected to because of the following informalities: The claim appears to be grammatically incorrect, see esp. lines 4-5. The "and" has been deleted in line 4, so it is unclear what the relationship is between what is listed in (a) relative to (b) of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 249, 250, 257 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 247 recites at least two domains. Claims 249 and 250 depend from claim 247, but claims 249 and 250 recite "said domain." It is unclear which of the two or more domains listed in claim 247 is the "said domain" in claims 249 and 250.

Claim 257 recites the limitation "said specific binding" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 245-255, 257-265, and 306 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al. (U.S. Patent 5,521,291).

Curiel et al. (U.S. Patent 5,521,291) teach methods, compositions, target cells for delivering compositions to cells in vitro and in vivo, and kits for target cell delivery, which compositions comprise a construct having at least one terminus comprising a polynucleotide tail hybridized to a complementary polynucleotide and an antibody bound to the hybridized polynucleotide (e.g. ribozymes attached to antibodies, or viral nucleic acids for target cell delivery in combination with antisense for target gene inhibition, target cell ligands), which constructs are optionally bound non-ionically to a ligand, and

compositions which optionally comprise a domain to a specific nucleic acid component and a domain to a cell of interest, and a different, specific nucleic acid desired to be delivered to said cell, and optionally comprising a binder which is optionally the same as the domain to a cell of interest, or a polylysine, or one which mediates ligand binding to a receptor, including lectins, antigens and other receptors (see esp. the abstract; Fig. 1; col. 3-11; 13; 16; example 6, col. 24-29; claims 3, 5, 6, 14 and 15).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 245-255, 257-260, 262-265 and 306 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 275, 289, 290, 296-301 of copending Application No. 08/978,634. Although the

conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to methods and cell delivery compositions comprising covalently bound polynucleotides, targeting ligands and polypeptides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 245-255, 257-260, 262, and 306 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of copending Application No. 11/929,897. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to cell delivery compositions comprising covalently bound polynucleotides, targeting ligands and polypeptides.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO

DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
9-19-08

/Jane Zara/
Primary Examiner, Art Unit 1635